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## METHOD OF BONDING TISSUE SURFACES AND CONTROLLING HEMORRHAGING THEREOF USING A TISSUE ADHESIVE AND HEMOSTATIC COMPOSITION

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11 Claims

### ABSTRACT OF THE DISCLOSURE

A method of bonding traumatized tissue surfaces and controlling hemorrhaging therefrom is disclosed. An adhesive comprising a mixture of a soluble proteinaceous prepolymer such as gelatin, a modifying agent in the form of a phenol derivative, and an aldehyde cross-linking agent is applied to the surfaces to be bonded and cross-linking is effected. The adhesive provides an extremely strong bond.

This invention relates to tissue adhesives and hemostatic agents and processes for using the same, and relates more particularly to improved systems for bonding traumatized tissue surfaces and controlling hemorrhaging therefrom.

Tissue adhesives have widespread potential applicability in surgery and recent interest in the applications of such materials has been widespread. The more promising suggestions of the prior art include cross-linked gelatin-formaldehyde systems, isocyanate polyurethane systems and cyanoacrylate systems. However, all of the materials currently available suffer from significant disadvantages.

In general, the desiderata commonly considered necessary for a fully satisfactory surgical adhesive might be listed as follows:

- (1) The bonding material should have high initial tack.
- (2) It should bond rapidly to living tissues.
- (3) The strength of the bond should not be altered by the presence of some degree of moisture.
- (4) The adhesive composition should be insoluble or only slowly soluble in bodily fluids.
- (5) The constituents of the composition should be relatively nonirritating locally, at least in the amounts required to effect the desired bond.
- (6) Similarly, the constituents should be relatively non-toxic systemically in the amounts necessary for use.
- (7) The strength of the bond should be of such a magnitude that tissue failure will occur under challenge before bond failure.
- (8) The bond should preferably be relatively flexible.
- (9) The tissue adhesion effected and the compositions themselves should be consistently uniform and reproducible from batch to batch.
- (10) The bonding materials should have good shelf life.

(11) The costs of the chemical constituents and procedures to be utilized should be relatively economical.

All of the commercial surgical bonding materials presently on the market fail to satisfy one or more of the above requirements. Quite frequently, such compositions have poor initial tack and decreased bond strength in the presence of moisture.

In order to be fully satisfactory as a biological cement or hemostatic agent, a surgical adhesive must be effective on moist, as well as relatively dry, tissue surfaces. Further, an ideal bond is characterized by the occurrence of tissue failure, with actual tearing away of the individual fibers from one and another, in contrast to be separation of the adhesive layer from the underlying tissue,

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more commonly seen when the presently available bonding means are used.

Certain of the surgical materials based on gelatinous sponges have a tendency to become mechanically, dislodged unless held in position for prolonged times necessary for a fibrin clot to entrap the sponge in the area of a trauma.

Finally, some of the prior art materials exhibit variable potency between batches and relatively poor shelf life.

Considering the above, it is a primary object of this invention to provide tissue adhesive and hemostatic compositions and procedures for using the same which satisfactorily provide all of the above desiderata and overcome the various disadvantages inherent with presently available prior art systems.

Thus, it is a basic object of this invention to provide a tissue adhesive and hemostatic agent and procedures for utilizing the same which will relatively rapidly provide high strength bonds between living tissues whether or not moisture is present in the environment. Further, it is a significant objective of this invention to provide a surgical adhesive of the type described which will form bonds on the order of magnitude of the cohesive forces possessed by the collagen which normally forms part of the cellular cement holding natural tissue cells together and which, in fact, is chemically similar to the connective tissue of the body thereby simulating naturally occurring fibers.

Another important object of the instant invention is the provision of an adhesive system utilizing small quantities of chemical constituents in amounts which are relatively non-irritating locally and relatively non-toxic systemically in the amounts required and wherein the adhesive is removed by body fluids after the tissue regenerates.

Additionally, it is a further object of this invention to provide an adhesive system having functional characteristics which may be consistently reproduced and which has good shelf life.

Still further, this invention contemplates the provision of various procedures for utilizing the tissue adhesives which are relatively simple, yet highly reliable and efficient, and which, in certain instances, provide techniques for obviating tissue irritation where the situs of the trauma is particularly sensitive.

Other and further objects reside in the combination of chemical constituents in the composition and in the functional characteristics of the same as well as in the manipulative steps of the procedures. Still other objects will in part be obvious and in part be pointed out as the description of the invention proceeds.

It has now been found that all of the above advantageous characteristics can be provided by utilizing a surgical adhesive and hemostatic agent composition according to this invention which is based on

(1) A soluble proteinaceous prepolymer which can be insolubilized to form a gel matrix, e.g., gelatin, collagen and artificial polypeptides,

(2) A cross-linking agent which cross-links the protein and binds it to the tissue, e.g., various aldehydes such as formaldehyde, glutaraldehyde, glyoxal, adipaldehyde and polyacrolein, and

(3) A water-resisting agent which reacts with the protein and the cross-linking agent to produce a water-insoluble polymer, thus rendering the gel water-resistant, e.g., phenol derivatives such as resorcinol, phloroglucinol, hydroquinone,  $\beta$ -naphthol and 1,3-dihydroxynaphthalene.

Although initial studies indicate the various above-listed materials will provide satisfactory results, the preferred adhesive consists of gelatin and resorcinol cross-linked with formaldehyde and therefore the major portion of this specification will be directed to this composition. However, it is to be understood that other equivalent materials such as those discussed above could be sub-